NEW DRUG APPROVALS

Crysvita for Rare Form of Rickets

Burosumab-twza (Crysvita, Ultragenyx Pharmaceutical, Inc.) has become the first FDA-approved drug to treat adults and children 1 year of age and older with x-linked hypophosphatemia (XLH), a rare inherited form of rickets.

XLH causes low levels of phosphorus in the blood, leading to impaired bone growth and development in children and adolescents and problems with bone mineralization throughout life. Vitamin D therapy is not effective for XLH, which affects approximately 3,000 children and 12,000 adults in the United States.

Burosumab's safety and efficacy were studied in four clinical trials. In the placebo-controlled trial, 94% of adults receiving burosumab once a month achieved normal phosphorus levels compared with 8% of those receiving placebo. In children, 94% to 100% of patients treated with burosumab every two weeks achieved normal phosphorus levels. In both children and adults, x-ray findings associated with XLH improved with burosumab therapy. Comparison of the results to a natural history cohort also provided support for the effectiveness of burosumab.

The most common adverse reactions in adults taking burosumab were back pain, headache, restless leg syndrome, decreased vitamin D, dizziness, and constipation. The most common adverse reactions in children were headache, injection-site reaction, vomiting, decreased vitamin D, and pyrexia.

Burosumab was granted FDA breakthrough therapy and orphan drug designations. The sponsor is receiving a rare pediatric disease priority review voucher.

Source: FDA, April 17, 2018

Tavalisse for Chronic Immune Thrombocytopenia

The FDA has approved fostamatinib disodium hexahydrate (Tavalisse, Rigel Pharmaceuticals, Inc.) for the treatment of thrombocytopenia in adults with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

Fostamatinib is an oral spleen tyrosine kinase inhibitor that targets the underlying autoimmune cause of the disease by impeding platelet destruction.

The approval was supported by a clinical program that included two randomized, placebo-controlled, phase 3 trials and an open-label extension, as well as an initial proof-of-concept study. The application included data from 163 ITP patients and was supported by a safety database of more than 4,600 patients across other indications in which fostamatinib has been evaluated.

In patients with ITP, the immune system attacks and destroys the body's own blood platelets, which play an active role in blood clotting and healing. Current therapies include steroids, blood platelet production boosters, and splenectomy, but not all patients have an adequate response to those treatments.

Source: Rigel Pharmaceuticals, April 17, 2018

Ilumya for Plaque Psoriasis

Tildrakizumab-asmn (Ilumya, Sun Pharmaceutical Industries Ltd.) has received FDA approval for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

Tildrakizumab selectively binds to the p19 subunit of interleukin (IL)-23 and inhibits its interaction with the IL-23 receptor, impeding the release of pro-inflammatory cytokines and chemokines. Tildrakizumab is administered at a dose of 100 mg by subcutaneous injection every 12 weeks, after the completion of initial doses at weeks 0 and 4.

The approval was supported by two phase 3 trials (reSURFACE 1 and reSURFACE 2), in which 926 adult patients were treated with tildrakizumab (n = 616) or placebo (n = 310). Both studies met the primary efficacy endpoints, demonstrating significant clinical improvement with tildrakizumab compared to placebo when measured by skin clearance of at least 75% (Psoriasis Area Sensitivity Index [PASI] 75) and Physician's Global Assessment (PGA) score of "clear" or "minimal" at week 12 after two doses. PASI 75 for tildrakizumab versus placebo was 64% versus 6% in reSURFACE 1 and 61% versus 6% in reSURFACE 2. PGA for tildrakizumab versus placebo was 58% versus 7% in reSURFACE 1 and 55% versus 4% in reSURFACE 2.

The most common adverse reactions associated with tildrakizumab are upper respiratory infections, injection-site reactions, and diarrhea.

Sun licensed worldwide rights to tildrakizumab from Merck & Co.; with Sun funding, Merck completed phase 3 trials and submitted the application to the FDA.

Source: Sun Pharma, March 21, 2018

Full Approval for Pradaxa

The FDA has given full approval to idarucizumab (Praxbind, Boehringer Ingelheim), the specific reversal agent for dabigatran (Pradaxa, Boehringer Ingelheim). Idarucizumab is indicated for patients treated with dabigatran when reversal of dabigatran's anticoagulant effects is needed for emergency or urgent procedures or in life-threatening or uncontrolled bleeding.

The FDA granted accelerated approval to idarucizumab in October 2015, with continued approval contingent on results of the phase 3 RE-VERSE AD trial. The final results of RE-VERSE AD showed that idarucizumab immediately reversed the anticoagulant effect of dabigatran. The majority of patients had complete reversal of anticoagulation within four hours as

measured by ecarin clotting time (82%) or diluted thrombin time (99%). No adverse safety signals were observed, and there was a low rate of thrombotic events.

In clinical studies, idarucizumab has not shown a procoagulant effect. Health care providers should consider resuming anticoagulant therapy as soon as medically appropriate due to the risk of thrombosis associated with patients' underlying conditions.

Source: Boehringer Ingelheim, April 17, 2018

Generic Approvals

Miglustat for Gaucher Disease

Amerigen Pharmaceuticals Ltd. and Dipharma S.A. have received FDA approval to market miglustat 100 mg capsules, the first generic equivalents of Actelion Pharmaceuticals' Zavesca. Miglustat is a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of adult patients with mild-to-moderate type-1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

Source: Amerigen Pharmaceuticals and Dipharma S.A., April 23, 2018

NEW INDICATIONS

Trelegy Ellipta for More COPD

The FDA has expanded the indications for fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta, GlaxoSmithKline/Innoviva) to include long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. It is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.

The approval is supported by the IMPACT study, which showed the medication was superior to two other combination drugs made by the same partners, fluticasone furoate/vilanterol (Breo Ellipta) and umeclidinium/vilanterol (Anoro Ellipta), on multiple clinically important endpoints, including reducing exacerbations and improving lung function and health-related quality of life.

Fluticasone furoate/umeclidinium/vilanterol was originally approved in the U.S. in September 2017 for the long-term, once-daily maintenance treatment of COPD patients who are receiving fluticasone furoate/vilanterol and require additional bronchodilation or who are receiving fluticasone furoate/vilanterol and umeclidinium (Incruse, GlaxoSmithKline/Innoviva). It is not indicated for relief of acute bronchospasm or for the treatment of asthma.

Fluticasone furoate/umeclidinium/vilanterol is the first COPD treatment to combine three molecules in a single once-daily inhalation. Fluticasone furoate is an inhaled corticosteroid (ICS), umeclidinium is a long-acting muscarinic antagonist, and vilanterol is a long-acting beta$_2$-adrenergic agonist (LABA); they are delivered in the Ellipta dry-powder inhaler.

The boxed warning has been removed from the product prescribing information in line with recent updates to the ICS/LABA class. Labeling changes to ICS/LABA combination medicines were implemented following a review of safety data submitted to the FDA by GlaxoSmithKline and two other companies.

Source: GlaxoSmithKline, April 24, 2018

Bydureon With Basal Insulin

Exenatide extended release (ER) for injectable suspension (Bydureon, AstraZeneca) has received FDA approval as an add-on therapy to basal insulin in adults with type-2 diabetes (T2D) with inadequate glycemic control. Exenatide ER is approved for adults with T2D whose blood sugar remains uncontrolled on one or more antidiabetic medicines, in addition to diet and exercise, to improve glycemic control.

The expanded use is based on results from the 28-week DURATION-7 study, which compared exenatide ER with placebo as add-on therapy to insulin glargine, with or without metformin, in adults with T2D. Mean hemoglobin A1c (HbA_{1c}) was reduced by 0.9% in the exenatide ER group (n = 231) compared with 0.2% in the placebo group (n = 229) in patients with a mean baseline HbA_{1c} of 8.5%. In addition, 32.5% of exenatide ER patients reached an HbA_{1c} of less than 7.0% compared with 7.0% of placebo patients. There were no new safety findings.

Source: AstraZeneca, April 3, 2018

Afinitor Disperz for Seizures In Tuberous Sclerosis Complex

Everolimus tablets for oral suspension (Afinitor Disperz, Novartis) have secured FDA approval for adjunctive treatment of adult and pediatric patients 2 years of age and older who have partial-onset seizures associated with tuberous sclerosis complex (TSC). It is the first approved pharmacological therapy in the U.S. specifically indicated for this rare genetic disorder.

The approval was based on the phase 3 EXIST-3 study, which found that when used as an adjunctive therapy, everolimus significantly reduced the frequency of treatment-resistant seizures associated with TSC compared with placebo.

The most common all-grade adverse events included stomatitis, diarrhea, nasopharyngitis, upper respiratory tract infection, and pyrexia.

Everolimus is also the only approved nonsurgical option indicated for treating TSC-associated noncancerous brain and kidney tumors. A kinase inhibitor, it hinders the mammalian target of rapamycin, a protein that regulates multiple cellular functions.

Source: Novartis, April 10, 2018

Tagrisso as First-Line Therapy for Some NSCLC

The FDA has approved osimertinib (Tagrisso, AstraZeneca) for the first-line treatment of patients with metastatic non–small-cell lung cancer (NSCLC) whose tumors have epidermal growth factor receptor (EGFR) mutations (exon 19 deletions or exon 21 L858R mutations), as detected by an FDA-approved test.

The approval is based on the FLAURA trial, which compared osimertinib to current first-line EGFR tyrosine kinase inhibitors (TKIs)—erlotinib (Tarceva, OSI Pharmaceuticals) or gefitinib (Iressa, AstraZeneca)—in previously untreated patients with locally advanced or metastatic EGFR-mutated (EGFRm) NSCLC.

Osimertinib met the primary endpoint of progression-free survival (PFS); its results were consistent across all prespecified patient subgroups, including those with or without central nervous system metastases. Safety data for osimertinib in FLAURA were in line with prior clinical trials. Osimertinib was generally well tolerated.

In the U.S., osimertinib was previously approved for the second-line treatment of patients with metastatic EGFRm NSCLC whose disease has progressed on or after a first-line EGFR TKI therapy and who have developed the secondary T790M mutation, as detected by an FDA-approved test.

AstraZeneca partnered with Roche Molecular Systems to develop the cobas EGFR Mutation Test v2 as the companion diagnostic for osimertinib. The diagnostic is simultaneously approved as a tissue- or plasma-based test to identify patients with EGFRm NSCLC who are eligible for first-line treatment with osimertinib and as a tissue or plasma-based test to identify patients with EGFR T790M mutation-positive NSCLC whose disease has progressed on a first-line EGFR TKI.

Source: AstraZeneca, April 18, 2018

Opdivo Plus Yervoy For Certain RCC Cases

The combination of nivolumab and ipilimumab (Opdivo and Yervoy, Bristol-Myers Squibb) has received FDA approval for the treatment of intermediate- or poor-risk, previously untreated advanced renal cell carcinoma (RCC).

The approvals were based on the randomized, open-label CheckMate 214 trial. Patients with previously untreated advanced RCC received nivolumab (3 mg/kg) plus ipilimumab (1 mg/kg) every three weeks for four doses followed by nivolumab monotherapy (3 mg/kg) every two weeks, or sunitinib (Sutent, Pfizer) 50 mg daily for four weeks followed by two weeks off every cycle.

Efficacy was evaluated in 847 intermediate- or poor-risk patients. The trial demonstrated statistically significant improvements in overall survival (OS) and objective response rate (ORR) among the 425 patients receiving the combination compared with the 422 receiving sunitinib. Estimated median OS was not estimable in the combination arm compared with 25.9 months in the sunitinib arm (hazard ratio, 0.63). The ORR was 41.6% for the combination versus 26.5% for sunitinib. The efficacy of the combination in patients with previously untreated RCC with favorable-risk disease was not established.

The most common adverse reactions were fatigue, rash, diarrhea, musculoskeletal pain, pruritus, nausea, cough, pyrexia, arthralgia, and decreased appetite.

The recommended schedule and dose for this combination is nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every three weeks for four doses, then nivolumab 240 mg every two weeks or 480 mg every four weeks.

Source: FDA, April 16, 2018

Rubraca for More Ovarian Cancer

The FDA has approved rucaparib (Rubraca, Clovis Oncology) for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. The agency granted regular approval for rucaparib in this second, broader, earlier-line indication, which does not require biomarker testing. The FDA also converted the approval of rucaparib's initial treatment indication from accelerated to regular approval.

The maintenance treatment approval is based on positive results from the phase 3 ARIEL3 study, which evaluated rucaparib among three populations: 1) *BRCA*-mutant (BRCAmut+), 2) homologous recombination deficiency-positive inclusive of BRCAmut+, and 3) all patients treated in ARIEL3. The study enrolled 564 patients. ARIEL3 achieved its primary and key secondary endpoints: extending investigator-assessed progression-free survival versus placebo in all patients treated, regardless of *BRCA* status.

The most common adverse reactions (mostly grade 1–2) included nausea, fatigue/asthenia, abdominal pain/distention, rash, dysgeusia, anemia, aspartate and alanine transaminase elevation, constipation, vomiting, diarrhea, thrombocytopenia, and nasopharyngitis/upper respiratory tract infection.

Rucaparib is an oral, small-molecule inhibitor of poly (ADP-ribose) polymerase 1 (PARP1), PARP2, and PARP3. In addition to the new maintenance indication, it is approved for the treatment of adults with deleterious *BRCA* mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies; they are selected for therapy based on an FDA-approved companion diagnostic.

Source: Clovis Oncology, April 6, 2018

Tasigna for Children With Rare Form of Leukemia

The FDA has expanded the indication for nilotinib (Tasigna, Novartis) to include first- and second-line treatment for pediatric patients 1 year of age or older with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP).

Nilotinib is now indicated for the treatment of adult and pediatric patients 1 year of age or older with newly diagnosed Ph+ CML-CP. It is also indicated for the treatment of pediatric patients 1 year of age or older with Ph+ CML-CP resistant or intolerant to prior tyrosine kinase inhibitor (TKI) therapy, as well as adults with Ph+ CML in chronic phase and accelerated phase resistant or intolerant to prior therapy that included imatinib.

In CML, the body produces malignant white blood cells. Almost all patients with CML have the Philadelphia chromosome, which produces a protein called BCR-ABL. This protein aids the proliferation of malignant white blood cells. CML accounts for about 3% of newly diagnosed childhood leukemia.

The new indications are based on two studies evaluating the efficacy and safety of nilotinib in patients 2 years to less than 18 years of age with Ph+ CML-CP. Sixty-nine patients, either newly diagnosed (first-line) or resistant or intolerant to prior TKI therapy (second-line), received nilotinib. In newly diagnosed patients, the major molecular response (MMR) rate was 60.0% at 12 cycles. The cumulative MMR rate among newly diagnosed patients was 64.0% by cycle 12, and the median time to first MMR was 5.6 months. In patients with resistance or intolerance to prior TKI therapy, the MMR rate was 40.9% at 12 cycles. The cumulative MMR rate among patients with resistance or intolerance was 47.7% by cycle 12, and the median time to first MMR was 2.8 months.

Adverse reactions were generally consistent with those observed in adults, except for laboratory abnormalities of hyperbilirubinemia and transaminase elevation, which were reported at a higher frequency than in adults.

Source: Novartis, March 22, 2018

Hizentra for CIDP

The FDA has approved immune globulin subcutaneous (human) 20% liquid (Hizentra, CSL Behring) as the first subcutaneous immunoglobulin (SCIg) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment.

The approval was based on the phase 3 PATH study. It demonstrated that the percentage of patients experiencing CIDP relapse or withdrawal for any other reason during SCIg treatment was significantly lower with Hizentra (38.6% on a low dose [0.2 g/kg weekly] and 32.8% on a high dose [0.4 g/kg weekly]) than with placebo (63.0%). Hizentra patients reported fewer systemic adverse reactions per infusion compared with intravenous Ig treatment (2.7% versus 9.8%, respectively).

In CIDP, a rare autoimmune disorder, the myelin sheath covering peripheral nerves is damaged. This may result in numbness or tingling, muscle weakness, fatigue, and other symptoms. CIDP effects can worsen over time, limiting activity and decreasing quality of life.

Source: CSL Behring, March 16, 2018

FDA REVIEW ACTIVITIES

Breakthrough Therapy Status

Trumenba for Invasive MenB Disease

The FDA has granted a breakthrough therapy designation to Pfizer's Trumenba (meningococcal group B vaccine). Trumenba is designed to prevent invasive disease caused by *Neisseria meningitidis* group B (MenB) in children ages 1 year through 9 years.

This is the first breakthrough therapy designation for a MenB vaccine to help protect children as young as 1 year old. Trumenba previously received breakthrough therapy designation in 2014 for the prevention of MenB in adolescents and young adults ages 10 years through 25 years, and later the same year the FDA gave it the first MenB vaccine approval in the U.S.

In an October 2014 approval letter, Pfizer was required to assess the safety and effectiveness of Trumenba in children as young as 1 year of age. Pfizer has successfully completed phase 2 studies in this investigational age group; the data supported Pfizer's request for breakthrough therapy designation.

Source: Pfizer, April 23, 2018

Hemlibra for Hemophilia A

Genentech has been granted a breakthrough therapy designation for Hemlibra (emicizumab-kxwh), a treatment for hemophilia A without factor VIII inhibitors.

Emicizumab is a bispecific factor IXa- and factor X-directed antibody designed to bring together factor IXa and factor X, proteins required to activate the natural coagulation cascade and restore the blood-clotting process for hemophilia A patients. Emicizumab is a prophylactic treatment that can be administered by an injection of a ready-to-use solution subcutaneously (SQ) once weekly.

The designation is based on data from a phase 3 study in people 12 years of age or older with hemophilia A without inhibitors. Emicizumab prophylaxis dosed SQ every week or every two weeks showed a statistically significant and clinically meaningful reduction in treated bleeds compared with no prophylaxis. In an intrapatient comparison, once-weekly emicizumab prophylaxis was superior to prior factor VIII prophylaxis as demonstrated by a statistically significant and clinically

meaningful reduction in treated bleeds. The most common adverse events with emicizumab were injection-site reactions, and no new safety signals were observed. No thrombotic microangiopathy or thrombotic events occurred.

Source: Genentech, April 17, 2018

OMS721 for Thrombotic Microangiopathy

The FDA has granted a breakthrough therapy designation to OMS721 (Omeros Corp.) for the treatment of patients with high-risk hematopoietic stem cell transplant-associated thrombotic microangiopathy (HSCT-TMA), specifically those patients who have persistent TMA despite modification of immunosuppressive therapy. This is the second breakthrough therapy drug designation for OMS721, which last year received the designation for the treatment of immunoglobulin A (IgA) nephropathy.

Persistent TMA is a life-threatening complication of HSCT. Approximately 20,000 HSCT procedures are performed in the U.S. annually, and TMA is reported to occur in approximately 10% to 25% of HSCT patients. Reported mortality in high-risk patients is greater than 90%. Currently, there is no approved treatment.

Breakthrough therapy designation was granted based on data from a phase 2 trial evaluating OMS721 in patients with high-risk HSCT-TMA. The estimated median survival for OMS721-treated patients was an order of magnitude greater than that for a matched historical control. OMS721-treated patients had improved survival relative to the historical control (53% versus 10%). Biomarkers of disease (i.e., mean platelet count and mean levels of lactate dehydrogenase and haptoglobin) demonstrated statistically significant improvement. Study patients also showed substantial improvement in red blood cell and platelet transfusion requirements.

OMS721 is also being evaluated in ongoing phase 3 trials in IgA nephropathy and atypical hemolytic uremic syndrome. Across all clinical trials with OMS721, the drug has been well tolerated, and no safety concerns have been identified.

Based on requests from physicians, Omeros has established a compassionate-use program for OMS721, which is active in both the U.S. and Europe.

Source: Omeros Corp., April 26, 2018

Fast-Track Designations

AAV-RPGR for Retinitis Pigmentosa

The FDA has granted a fast-track designation for AAV-RPGR (MeiraGTx Ltd.), a gene therapy for the treatment of x-linked retinitis pigmentosa (XLRP) due to defects in the retinitis pigmentosa GTPase regulator gene (*RPGR*).

XLRP represents the most severe form of retinitis pigmentosa (RP), a group of inherited retinal diseases characterized by progressive retinal degeneration and vision loss that results in complete blindness. There are currently no approved treatments for RP. The most frequent mutation causing XLRP is in *RPGR*, accounting for more than 70% of cases of XLRP and up to 20% of all cases of RP.

MeiraGTx is conducting an open-label, phase 1/2, dose-escalation clinical trial of AAV-RPGR in adult and pediatric patients diagnosed with XLRP, as well as an ongoing natural history study of patients with XLRP.

Source: MeiraGTx, April 23, 2018

SYNB1618 for Phenylketonuria

The FDA has granted a fast-track designation to SYNB1618 (Synlogic, Inc.), an oral investigational medicine for phenylketonuria (PKU).

PKU is an inborn error of metabolism caused by a defect in the gene encoding phenylalanine hydroxylase, a liver enzyme that metabolizes Phe, an essential amino acid that can be toxic if it accumulates in the blood and brain. Current disease management of PKU involves strict dietary protein restriction with Phe-free protein supplements. The only currently approved medication, sapropterin dihydrochloride (Kuvan, BioMarin Pharmaceutical), is indicated for a subgroup of patients and does not eliminate the need for ongoing dietary management. Despite the diet, patients typically experience worsening neurological function depending on the severity of their genetic mutation and their treatment compliance.

SYNB1618 is a synthetic biotic medicine engineered to execute a programmed metabolic pathway designed to consume Phe and convert it into harmless metabolites.

Source: Synlogic, April 25, 2018

Orphan Drug Designation

EH301 for ALS

Elysium Health has been granted an orphan drug designation for EH301 for the treatment of amyotrophic lateral sclerosis (ALS), which affects nerve cells that control voluntary muscles. As muscles become weak and eventually paralyzed, most people with ALS succumb to respiratory failure, usually within three to five years from when symptoms first appear.

The submission included data from a 2017 European pilot study. To expand on the results of that study, Elysium Health expects to initiate a placebo-controlled study in collaboration with Mayo Clinic to evaluate EH301 in up to 150 adults with ALS by the fourth quarter of 2018.

Source: Elysium Health, March 29, 2018

DRUG SAFETY ISSUES

Lamictal Immune Reactions

The FDA warns that lamotrigine, used to treat seizures and bipolar disorder, can cause a rare but very serious reaction that excessively activates the body's infection-fighting immune system. This can cause severe inflammation throughout the body and lead to hospitalization

and death, especially if the reaction is not diagnosed and treated quickly. The agency is requiring that a warning about this risk be added to the lamotrigine prescribing information.

The immune system reaction, hemophagocytic lymphohistiocytosis (HLH), causes an uncontrolled response by the immune system. HLH typically presents as a persistent fever, usually greater than 101° F, and it can lead to severe problems with blood and organs throughout the body. Diagnosis is often complicated because early signs and symptoms, such as fever and rash, are not specific.

Lamotrigine has been on the market for 24 years and is available under the brand name Lamictal (GlaxoSmithKline) and as generics.

Health care professionals should discontinue lamotrigine if HLH or another serious immune-related adverse reaction is suspected and an alternative etiology for the signs and symptoms cannot be established.

Source: FDA, April 25, 2018

FDA Reviewing Nuplazid

The FDA is reviewing the safety of pimavanserin (Nuplazid, Acadia Pharmaceuticals) after reports of side effects, including deaths, among patients who take it for psychosis related to Parkinson's disease.

In April, a CNN report said hundreds of patients died after receiving pimavanserin, and FDA Commissioner Scott Gottlieb, MD, told lawmakers he'd "take another look" at the drug after they grilled him about it at a hearing on Capitol Hill. In November 2017, the Institute for Safe Medication Practices documented 244 deaths between pimavanserin's launch in June 2016 and March 2017. The FDA has tracked more than 700 deaths since patients began receiving the medication.

Acadia stands by the safety of its drug, which was approved in April 2016 with a boxed warning. "As the only drug currently approved by the FDA for the treatment of hallucinations and delusions associated with PDP [Parkinson's disease psychosis], Nuplazid is filling an important and previously unmet need and offers hope to those with PDP and the people who care for them," the company said on its website. "We remain confident in the efficacy and safety of Nuplazid that supported its approval by the FDA and stand firmly behind it."

At an FDA panel review in 2016, experts voiced concerns about the pimavanserin data, but many said the drug would treat patients with no alternatives—patients who'd be willing to take the risks associated with the therapy. The FDA's own reviewers raised questions about safety and efficacy ahead of the meeting.

Source: *FiercePharma*, April 26, 2018

DEVICE SAFETY ISSUES

Essure Restrictions

The FDA has restricted the sale and distribution of the Essure permanent contraception device (Bayer) to ensure that all women considering its use receive adequate risk information so that they can make informed decisions.

The agency acted after learning that some women were not adequately informed of risks associated with Essure before it was implanted, despite previous efforts to educate patients and doctors about those risks. The FDA is using its authority to restrict the sale and distribution of a device to impose additional requirements needed to provide a reasonable assurance of safety and effectiveness.

The new Essure labeling restricts the sale and distribution of the device to health care providers and facilities that provide information to patients about its risks and benefits. The health care provider must review a patient brochure, "Patient–Doctor Discussion Checklist—Acceptance of Risk and Informed Decision Acknowledgement," with the prospective patient to ensure the patient understands the risks, benefits, and other information about Essure implantation. The patient must be given the opportunity to sign the acknowledgment, and it must be signed by the physician implanting the device.

Bayer was ordered to implement the restrictions immediately and make sure that the process results in health care provider compliance. The FDA will review, monitor, and enforce Bayer's plans to ensure compliance.

To implant Essure, a health care provider inserts flexible coils through the vagina and cervix into the fallopian tubes. Tissue builds up around the inserts, creating a barrier that keeps sperm from reaching the eggs. Some patients implanted with Essure have experienced adverse events, including perforation of the uterus or fallopian tubes, migration of inserts to the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions.

The FDA approved Essure in 2002. In February 2016, the agency ordered Bayer to conduct a post-marketing study to better evaluate Essure's safety profile. In November 2016, the FDA mandated a boxed warning for Essure about adverse events, "including perforation of the uterus and/or fallopian tubes, identification of inserts in the abdominal or pelvic cavity, persistent pain, and suspected allergic or hypersensitivity reactions." The FDA also required that a more comprehensive patient decision checklist be added to the device labeling to give women considering Essure information about the benefits and risks of this device before deciding to use it.

Source: FDA, April 9, 2018

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MR Thermometry

The FDA is evaluating data suggesting that potentially inaccurate magnetic resonance (MR) thermometry information can be displayed during MR-guided laser interstitial thermal therapy (MRgLITT).

MRgLITT devices are used in neurosurgical procedures for minimally invasive ablation of brain tumors, epileptic foci, or radiation necrosis. MR thermometry is used to monitor the changes in temperature at the treatment site. However, MR parameters such as voxel size and MR image acquisition time may contribute to inaccurate MR thermometry readings and potential errors in ablation assessment. In addition, MRgLITT devices may not account for the continued thermal spread of energy to the surrounding tissue.

Medical device reports and literature describe adverse events, such as neurological deficits, increased intracerebral edema or pressure, intracranial bleeding, and/or visual changes, when these devices were used to treat intracranial lesions. Several events required urgent medical or surgical intervention and may have been associated with deaths, but it is unclear whether inaccurate MR thermometry contributed to these events.

The FDA recommends that health care providers consider and discuss with patients the benefits and risks of these devices, as well as the availability of alternative treatment modalities. The agency provides suggestions to improve safety while using the devices.

Source: FDA, April 24, 2018 ■